Cancer Lab BRCA - Teacher's Notes - Bioinformatics Study to Locate BRCA Cancer Genes

Alignments:

Patient A is a 33 year old mother of 4 children, 2 boys and 2 girls. Her mother and grandmother died of ovarian cancer at ages 54 and 48, respectively, and her aunt died of breast cancer at age 45. (She has been diagnosed with ovarian cancer at age 36 and continues to be treated.)
(17 bp deletions beginning on Sbjct row 301)
Note*:* Score = 1739 bits (1928), Expect = 0.0, Identities = 984/1001 (98%), Gaps = 17/1001 (2%), Strand = plus/plus will be what you will see across the top of the DNA strands. The query line is the BRCA1 DNA strand and the subj (subject) line is the patient's DNA strand. If you see dashes in the subject line as you scroll down, that means there were deletions in the patient's DNA. Since there are no other dashes except on subject row 301, then you can go to the Gaps = 17/1001 and know there are 17 deletions.

Patient B is a 47 year old man that is of Ashkenazi Jewish descent. (He was diagnosed with breast cancer at age 52 and just began treatment.)
(6bp insertions beginning on Sbjct row 481)
Note: Score = 1790 bits (1984), Expect = 0.0, Identities = 1001/1007, Gaps = 6/1007 (1%), Strand = plus/plus will be what you will see across the top of the DNA strands. The query line is the BRCA1 DNA strand and the subj (subject) line is the patient's DNA strand. If you see dashes in the query line as you scroll down, it means there were insertions in the patient's DNA. Since there are no other dashes except on subject row 481, then you can go to the Gaps = 6/1007 and know there are 6 insertions.

Patient C is a 56 year old woman with no children. She eats a diet of lean meat, whole grains and lots of fruits and vegetables, and walks 4 miles a day. (She does not have breast or ovarian cancer.)
There are no mutations in this gene.
Score = 1806 bits, Expect = 0.0, Identities = 1001/1001 (100%), Gaps = 0/1001 (0%), Strand = plus/plus will be what you will see across the top of the DNA strands. Since it 100% in alignment, the patient's DNA is identical to the BRCA1 DNA which means there are no mutations.

Patient D is a 65 year old mother of 2 children, a boy and a girl, and 5 grandchildren, 3 boys and 2 girls. She has smoked for 45 years. (She has been diagnosed with breast cancer at age 68 and continues to be treated.)
There are no mutations in this gene.
Score = 1806 bits (2002), Expect = 0.0, Identities = 1001/1001 (100%), Gaps = 0/1001 (0%), Strand = plus/plus will be what you will see across the top of the DNA strands. Since it 100% in alignment, the patient's DNA is identical to the BRCA1 DNA which means there are no mutations.

Patient E is a 45 year old woman whose father died from breast cancer at the age of 52. She has 3 children, 1 boy and 2 girls, and 1 grandchild, a girl. (She does not have breast or ovarian cancer but will have her children tested and depending on the results, perhaps the grandchild as well.)
(2bp insertions and 2 bp deletions beginning on Sbjct row 721)
Score 1786 bits (1980), Expect = 0.0, Identities = 999/1003 (99%), Gaps = 4/1003 (0%), Strand = plus/plus will be what you will see across the top of the DNA strands. The query line is the BRCA1 DNA strand and the subj (subject) line is the patient's DNA strand. If you see dashes in the subject line as you scroll down, that means there were deletions in the patient's DNA. If you see dashes in the query line as you scroll down, it means there were insertions in the patient's DNA. In row 721, there are insertions in the query line and deletions in the subject line, evenly divided. Since the Gaps=4/1003, there were 2 insertions and 2 deletions.

1. **When you aligned the patients' sequences compared to the normal *BRCA1* gene, what type(s) of mutation(s) did you observe in Patients A, B, C, D, E? Explain how you came to your conclusions.**

Patient A has a 17bp deletion. There are 17 base pairs in a row that are missing in Patient A's *BRCAI* gene.
Patient B has a 6 bp insertion. There are 6 extra base pairs in a row in Patient B's *BRCA 1* gene.
Patient C has no mutation. It exactly matches the *BRCA1* gene.
Patient D has no mutation. It exactly matches the *BRCA1* gene
Patient E has a 2bp insertion and a 2 bp deletion. There are 2 extra base pairs in a row and further down the same row of base pairs, there are 2 base pairs missing in Patient E's *BRCA1* gene.

2. **When a mutation occurs within the *BRCA1* gene, or any gene, what happens when the protein is transcribed and translated from the mutated gene?**

   The mutated DNA with deletions and/or insertions would be transcribed into mRNA which would cause the codon reading frame to shift as it translated the mRNA into protein. This would result in an abnormal protein in which the amino acids would not be the same type and in the same order as those in the protein encoded from the normal gene. This would cause the abnormal protein to fold in a new way which may or may not have active sites that are functional.

3. **Do all individuals who have inherited the *BRCA1* mutation develop breast or ovarian cancer? Why or why not?**

   No. The reason is not clear. If only one of the two inherited genes has a mutation, perhaps the normal gene codes for proteins that repair enough DNA to keep cancer from forming. Or, it could be that the damaged unrepaired DNA is recognized by the immune system and destroyed before it can develop into a cancerous tumor. Those who do develop cancer may have inherited two copies of the mutant gene (BB) or have inherited the heterozygous (Bb) version and a spontaneous mutation in the normal gene (b) occurred due to natural or environmental factors as they lived their lives. With two mutated genes, damaged DNA is not able to be repaired.

   In *BRCA1* genes, 1000 mutations have been found and many are associated with an increased risk of breast or ovarian cancer. In *BRCA2* genes, 800 mutations have been found and lead to a high incidence in breast cancer. In both, the mutations can be insertions or deletions of DNA. Only about 60% of the women who have inherited a harmful mutation in the *BRCA1* or *BRCA2* genes will develop breast cancer and only 15 – 40% will develop ovarian cancer.

4. **Should Patient A's children be tested for mutations in the *BRCA1* gene? Why or why not?**

   The decision to be tested is a very individual and personal one. Some people want to know and others don't. If a clearly defined mutation can be identified in the family line, then the information might be helpful to the parents as they care for their children. If not, the testing might result in murky results and make it even more difficult to decide on a course of action.

   A genetics counselor might advise testing for an individual if there is a family history of breast and/or ovarian cancer. This would include the incidence of breast cancer in two 1st degree relatives (mother, daughter, sister), in three or more 1st or 2nd degree relatives (grandmother or

aunt), in a 1st degree relative diagnosed at age 50 or younger, in a 1st degree relative with cancer in both breasts, in a male relative, in a 1st or 2nd degree relative diagnosed with both breast and ovarian cancer, or of Ashkenazi Jewish ancestry with any 1st degree relative with breast cancer or two 2nd degree relatives on the same side of the family is diagnosed with breast or ovarian cancer. Without having further information, it would seem that Patients C and D decided to be tested unnecessarily.

5. **Other than mutations in the *BRCA1* gene, what factor(s) can contribute to the development of breast or ovarian cancer?**

   In the general population (no *BRCA1* mutation), about 12% of women will develop cancer sometime in their life. Factors that can contribute to development of breast, ovarian cancer, and other types of cancers are:

   Age
   Smoking
   Heavy consumption of alcohol
   Combining smoking and heavy drinking
   Diet high in fat and sugar and low in vegetables and fruits
   Lack of regular exercise
   High (unrelenting) stress

6. **Summarize important points from this activity.**

   - Mutations cause a reading frame shift in translation of the protein resulting in an amino acid sequence which folds into a protein which may or may not be functional.
   - The decision to be tested for a *BRCA1* gene mutation is very personal and would depend on the family history.
   - Men and women who inherit a *BRCA1* gene mutation can develop breast cancer and women can develop ovarian cancer but not everyone who inherits the mutation will develop cancer.
   - Men and women who do not have a *BRCA1* gene mutation can develop breast cancer and women can develop ovarian cancer. Taking care of oneself by eating a healthy diet, exercising regularly, not smoking, and managing stress can help decrease the chance of developing any type of cancer over one's lifetime.

Teacher's Notes on Bioinformatics lab were developed by Lynda Jones, MS, ONPRC.